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Subcutaneous Implants of Polypropylene Filaments

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Summary

Extruded filaments of unmodified polypropylene (PP) with and without antioxidant were implanted subcutaneously in hamsters in order to determine their rate of degradation. Specimens were removed periodically during a 5 month test period and analyzed by infrared spectroscopy and dynamic mechanical testing. The analyses show that degradation begins to occur after only a few days. Although the reaction sequence is not known, several factors suggest that the *in vivo* degradation process is similar to autoxidation which occurs in air or oxygen.

The infrared data indicate that the hydroxyl content of the implants increases at a rate of 0.061 mg/g polypropylene per day during the initiation phase of the reaction. An induction time of 108 days was established. Carbonyl bonds appear after an implantation time of 50-90 days and increase thereafter. Mechanical tests indicate a decrease in the dynamic loss tangent, $\tan \delta$, during the first month of implantation for unmodified polypropylene. No change in the infrared spectra or $\tan \delta$ was observed, however, for implants containing an antioxidant.

Thus, it is apparent that polypropylene filaments implanted subcutaneously in hamsters degrade by an oxidation process which is retarded effectively by using an antioxidant. While the findings reported are specific to subcutaneous polypropylene implants, they suggest that degradation of other systems may involve similar processes. This notion suggests directions for further research on increasing the *in vivo* stability of synthetic polymers.

Long-term effects of polymer implantation upon tissue were not studied in this work.

INTRODUCTION

Because synthetic polymeric materials are now widely being used for the repair or replacement of diseased or destroyed parts of the

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body, there is considerable interest in the design of polymers for specific replacement tasks. In order to design and evaluate candidate materials for implantation, there are three major factors which must be considered,¹ namely: 1) matching the engineering properties of the candidate material with those of the tissues which it is to replace; 2) the effect of the implant on the biological environment; and 3) the effect of the biological environment on the properties of the implant material. The first of these deals with selecting a replacement material which has the same strength, flexibility, and other physical properties as the original material. Techniques for systematically matching properties for a desired replacement task are just now being developed.^{2,3}

Studies of the effects of the biological system upon polymers are relatively sparse. It has been shown that the tensile properties of polymers change after implantation for prolonged periods.⁴⁻⁷ It is also known that chain scission begins to occur in polymers shortly after implantation, though its affect upon mechanical properties may not be observed for much longer times.⁸ Very little is known about the mechanisms for change in the polymers. Certainly, a number of possibilities must be considered, depending on the specific polymer. Hydrolysis in polyesters and polyurethanes is possible due to presence of hydrogen ions and water in both body tissues and fluids.⁹ Also, the presence of oxygen in various forms makes the body a potentially powerful oxidizer to polymers which are susceptible to oxidation.

In this paper, we report on a study which was conducted to examine the role of oxygen in the reaction between a typical hydrocarbon-type polymer and the body. The objectives of the study were to determine 1) the length of time required for observable degradation to occur; 2) the type of degradation products formed; 3) the rate of degradation; and 4) the effect of the presence of an antioxidant on degradation and the rate of degradation.

MATERIALS AND METHODS

Choice of Polymer

Polypropylene (PP) was chosen as a representative polymer for this study for several reasons. Chemically, it is a simple carbon-backbone polymer, since it is composed solely of carbon and hydrogen.

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It is readily available as a pure material free of contaminants. It has excellent mechanical properties and it withstands steam sterilization. It contains no plasticizers which could react harmfully with the body or which might be lost during steam sterilization.

The most important property of polypropylene for this study, however, is that it is easily oxidized in its pure form. By studying any chemical and physical changes which the polymer undergoes with implantation, one can begin to relate the degree to which oxygen is involved in *in vivo* degradation of the polymer.

Polymer Preparation

Two samples of polypropylene were obtained from Hercules Company (Wilmington, Delaware). Both of them are basically the same with B a processed form of A, blended with an FDA-approved proprietary stabilizer system. The specifications of the samples are listed in Table I.

The polymer samples were fabricated into monofilaments by using an Instron capillary extrusion rheometer at an extrusion temperature of 200°C and an ambient quench temperature of approximately 25°C. The polymer melt resided in the rheometer for approximately 5 min before extrusion began. During this time, air bubbles were displaced from the melt by the force of a ram in order to minimize bulk thermal autoxidation which could have occurred due to the presence of air trapped in the melt. The filaments were drawn to the desired diameters by attaching the extrudate to a spool which was turned manually at various speeds until the required amount of filament was obtained. Total extrusion time for each of the samples was approxi-

TABLE I
Polypropylene Sample Specifications

Specification	A	B
M_w	314,000	280,000
(M_w/M_n)	7.85	7
Isotacticity (%)	96-97.5	96-97.5
Crystallinity (%)	50-65%	50-65
Stabilizer	Phenolic antioxidant (trace)	Hindered phenolic antioxidant and sulfur-containing synergist

mately 20 min. Intrinsic viscosities and infrared spectra of the polymer were obtained before and after extrusion to determine if molecular weight changes and/or autoxidation had occurred. Diameters for both A and B filaments were in the range of 0.1–0.3 mm, depending on the draw rate. Crystallinity of the extruded filament was not determined. All filaments were stored in a vacuum desiccator prior to use in order to prevent oxidation. Prior to implantation, the filaments were sterilized by exposure to an atmosphere of ethylene oxide for a period of 1 hr.

The Syrian golden hamster was chosen as the host animal for the implantation studies. The implants were made subcutaneously by the following surgical technique. A filament was threaded through the eye of a needle which was then drawn under the skin of the back of the hamster. The filament was cut from the needle so that, upon spreading the skin across the back of the hamster, the ends of the filament were drawn inside the skin. Filaments implanted by this technique remained undisturbed in the hamster for periods as long



Fig. 1. Photograph of a PP filament being implanted subcutaneously in a Syrian golden hamster.

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as the life-span of the animal. Figure 1 illustrates the method which was used.

Infrared spectroscopy of KBr pellets containing polypropylene was used to measure any increase in hydroxyl or carbonyl content which might occur in the polymer. The polymer samples were prepared for infrared spectroscopy by chopping the filaments into thin slices. A weighed amount of KBr was thoroughly mixed with the PP and subsequently transferred to a pellet die. The die had been previously heated in an oven to remove adsorbed water vapor.

The pellets were formed by connecting the die to a vacuum pump and subjecting the KBr-PP mixture to approximately 20,000 lb ram force in a laboratory press for approximately 1 min. The pellets were then removed from the die and stored in a vacuum desiccator until the infrared scans were made. A Perkin-Elmer model 180 spectrophotometer was used for obtaining the infrared spectra. Reference pellets for each sample were pressed immediately after the sample pellets were made. The same procedure was used in both cases, and an identical amount of KBr was used for the reference as for the sample.

The Rheovibron Dynamic Viscoelastometer Model DDV II (Vibron) was used to test mechanical properties. The purpose of the Rheovibron is to measure the temperature-dependence of the complex modulus of polymers at four fixed frequencies, 3.5, 11, 35, and 110 Hz.¹⁰ A sinusoidal tensile strain is applied at one end of the sample and a sinusoidal stress is generated at the other end. The phase angle, δ , between the applied strain and the resultant stress is measured and read off directly on a meter. The tangent of the phase angle, δ , was measured over a temperature range of 22–50°C. To illustrate concisely the trends observed, only the $\tan \delta$ data for 37°C and 3.5 Hz are included in this paper.

Gel-permeation chromatography (GPC) analyses of selected filaments were conducted using a Waters Model 200 gel-permeation chromatograph operating at 140°C using 1,3,5-trichlorobenzene as a solvent. Solutions of the samples were prepared having a concentration of approximately 0.1 wt %; 2 cc of this solution were used to perform analyses. From the GPC analyses, weight-average molecular weight, \bar{M}_w , number-average molecular weight, \bar{M}_n , and the molecular weight distribution curves were obtained for implanted and nonimplanted filaments.

RESULTS

Molecular weights of the polymer determined before and after extrusion showned no change in molecular weight. Infrared spectra showed no differences in hydroxyl content between the initial samples and the extruded filaments.

Figure 2 shows a plot of hydroxyl concentration [OH] versus implant time for A and B filaments. As shown in Figure 2, for the A filaments [OH] increases rapidly during the preinitiation period, then increases linearly with implantation time up to an implantation time of about 100 days. At this point, the slope changes and [OH] increases at a greater rate. Figure 3 shows carbonyl absorbance plotted versus implantation time for each of the A implants. It can be seen from Figure 3 that a time of 50–90 days passed before any measurable carbonyl formed. The exact length of this time is only estimated, since no data were taken between 49 and 99 days.

As shown in Figure 2, the value of [OH] for the B filaments did not change significantly. Similarly, no increase in carbonyl was observed for B filaments following implantation.

The results of dynamic mechanical testing of implanted filaments are shown in Figure 4, which is a plot of $\tan \delta$ versus implantation time for both A and B filaments. $\tan \delta$ decreased initially for the A filaments and then stabilized. No change was found for B filaments.

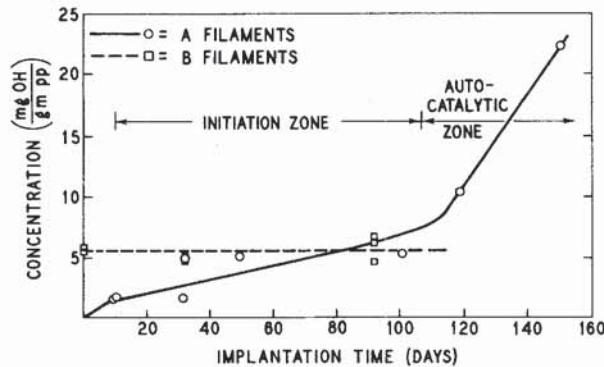


Fig. 2. Plot of hydroxyl concentration [OH] vs. implantation time for A and B filaments.

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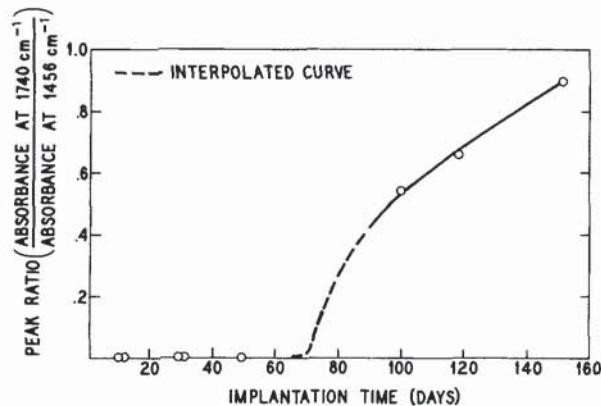


Fig. 3. Plot of carbonyl absorbance vs. implantation time for pure PP implants.

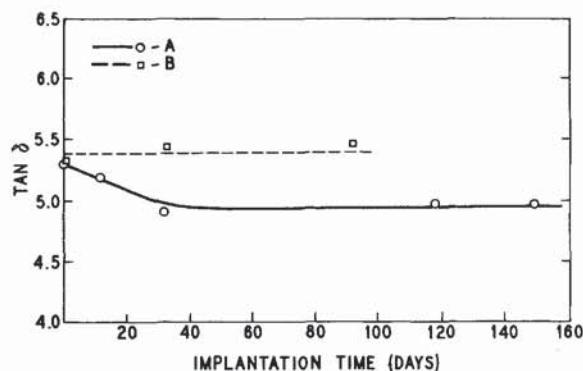


Fig. 4. Plot of tan δ vs. implantation time for A and B filaments. Temperature, 37°C; frequency, 3.5 Hz.

GPC analyses were performed on two samples of PP. The first sample was a 48 mg PP filament which had not been implanted. The second was prepared by combining three filaments implanted subcutaneously in separate hamsters for 70 days. Figure 5 shows the GPC molecular weight distribution curves obtained for both samples. From the GPC analyses shown in Figure 5, it can be seen that a slight shift in molecular weight distribution occurred. At the high molecular weight end of the curve, a decrease in the amount of very large molecules ($>3 \times 10^6$) resulted in an increase in the

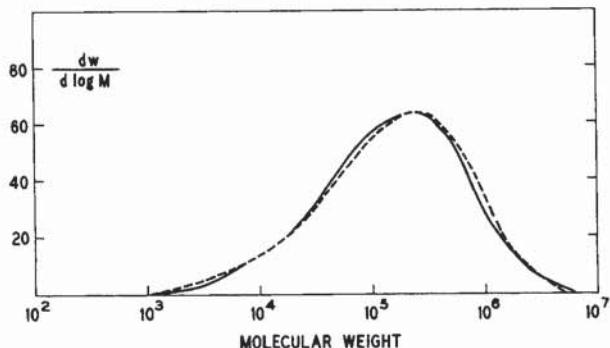


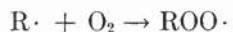
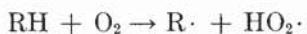
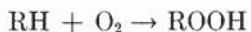
Fig. 5. Molecular weight distribution curves for A filaments: (—) before implantation; (- -) after implantation.

amount of medium-range molecules (3×10^5 to 3×10^6). At the lower end of the curve, an increase in the number of smaller molecules (10^3 to 10^4) corresponded to a decrease in the molecules of intermediate size (10^4 to 3×10^5).

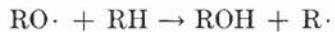
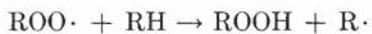
DISCUSSION

Polypropylene degrades at high temperatures in the presence of oxygen by a free-radical mechanism similar to that proposed by Bolland for the oxidative degradation of carbon-backbone polymers.¹¹ The exact mechanism is still a matter of speculation, but the following steps are considered to be important in the overall scheme:¹²⁻¹⁴

Initiation:



Propagation:



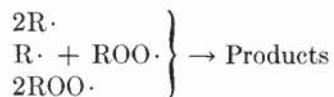
Radical transfer:



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Termination by coupling:



The initiation step has an activation energy of 31 kcal/mole,¹⁴ and is generally discussed in terms of an induction time θ which is a function of temperature and oxygen concentration. During this period, hydroperoxides (ROOH) are formed. When the hydroperoxides begin to decompose, chain scission occurs, causing carbonyl groups to form. Rapid oxidation then follows, causing a sharp increase in carbonyl content and a significant loss of tensile properties.¹⁵ The activation energy of this secondary oxidation has been found to be 22 kcal/mole.¹⁴ By plotting mg O₂ absorbed versus time, the induction time can be found by locating the intersection of the initiation and the autocatalytic portions of the curve.

Oswald and Turi¹⁵ found that at 75°C and in the presence of a 100% oxygen atmosphere, polypropylene tensile specimens degraded according to the same thermal oxidative degradation scheme proposed by others as a result of studies at higher temperatures.¹⁴ Provided that the oxidation data of other researchers may be extrapolated to body temperature, 37°C, an estimate of the induction time for the gas-solid phase oxidation of PP may be calculated. For PP oxidation at 37°C in 100% O₂, this procedure predicts an induction time of 242 days and an initiation rate of 0.0089 mg OH/g PP/day.

Although tissue oxygen concentration was not measured, based on measurements by others of the p_{O₂} in the hamster cheek pouch membrane,¹⁶ an approximate value of 25 mm Hg for the p_{O₂} of oxygen in subcutaneous tissue is useful for comparative purposes. Since the antioxidation reaction is proportional to oxygen concentration,¹⁴ the predicted initiation rate for oxidation of PP at 37°C in 3.3% O₂ is approximately 2.9×10^{-4} mg OH/g PP/day, and the induction time is estimated to be 20 years.

The gradual increase in hydroxyl (or hydroperoxide) content which occurs in the case of thermally autoxidized PP was also found to occur in the implanted filaments studied in this work. The presence of an induction time θ was also observed. The induction time corresponds to the intersection of the two lines approximating the initiation and propagation steps involved in the formation of hydroperoxide (meas-

ured by hydroxyl), as shown in Figure 2. Using this criterion, an induction time of 108 days was found for the pure PP filaments implanted in this work. In addition, from the slope of the first line which represents the initiation step (determined by a least-squares fit), a rate of formation of hydroxyl of 0.061 mg OH/g PP/day was found.

Figure 6 shows the differences between the observed oxidation reaction for implanted filaments and the autoxidation reaction predicted by extrapolating the thermal autoxidation data to 37°C for 100% O₂ and for 3.3% O₂. The superposition of the three curves shown in Figure 6 illustrates the greater oxidation rate which occurs for the implanted filaments.

These differences are probably due to some extent to the effect of surrounding fluids in the case of the implanted filaments. It is possible that trace amounts of metallic ions, enzymes, and other chemicals presented in the fluids surrounding the implanted tissue accelerate the oxidation reaction. However, it also has been stated by others¹⁵ that extrapolation of thermal autoxidation data to temperatures below 50°C is unwarranted. This is based on the fact that PP oxidizes in air at 25°C faster than extrapolation of thermal autoxidation data predicts. This may result from oxygen being more effective in producing chain scission at lower temperatures.¹⁵

Autoxidation occurs by the diffusion of oxygen into the amorphous interlamellae regions of the polymer. Scission of the interlamellae

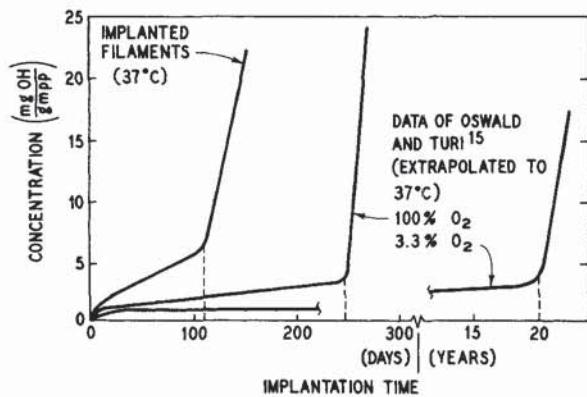


Fig. 6. Plot of [OH] vs. implantation time.

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molecules which join the crystalline regions caused the polymer to become brittle and ultimately fail with applied stress.^{15,17} It has been shown¹⁴ that PP autoxidation is a diffusion-controlled process for films of thickness greater than 0.13 mm. Since the filaments used in this study were thicker than the minimum thickness for diffusional control, it is reasonable to argue that the effects observed in this study were surface effects only. Further work is necessary to determine the importance of diffusion, and hence of crystallinity and orientation on the heterogeneous degradation of polypropylene implants.

The decrease in $\tan \delta$ with implantation time implies an increase in rigidity of the filament, a fact which verifies in mechanical terms the oxidation observed by infrared spectroscopy. The work of other researchers indicates that significant embrittlement does not occur during the initial phase of the oxidation process. Chain scission and embrittlement should occur only during the later stages of oxidation and have been found to be a function of the number of carbonyl groups formed.^{17,18} For the case of implanted A filaments, such a theory predicts a decrease in $\tan \delta$ coinciding with the first appearance of carbonyl groups. The curve in Figure 3 indicates that formation of carbonyl occurred between 50 and 90 days of implantation. However, no decrease in $\tan \delta$ was observed during that period.

Several reasons can be advanced to account for these differences. Certainly, experimental error cannot be discounted, since insufficient data points were taken to completely affirm the statistical significance of the results. Differences between the oxidation mechanisms could account for the observed behavior of $\tan \delta$ with time. Possibly, the filaments were stretched or otherwise physically altered during the implantation and removal phases of the experiments, causing the value of $\tan \delta$ to decrease.

The differences between the two molecular weight distribution curves in Figure 5 appear to be minor. However, the sensitivity of the GPC is such that slight differences such as those shown may be significant. The shifts to lower molecular weights observed are consistent with the view that some chain scission has occurred during the first 70 days of implantation. According to the infrared results shown in Figure 3, the amount of chain scission caused by carbonyl formation should be slight. Some measurable change in molecular weight distribution is not unexpected, however, since the time at which time carbonyl formed was only estimated by interpolation.

GPC analyses of filaments implanted for longer periods are necessary to confirm the results suggested here.

No changes in mechanical properties or infrared spectra were observed for any of the filaments containing antioxidant which were implanted. This indicates that the effects observed for the pure filament were not due to diffusion of chemical or fluids into the filaments. Since the antioxidant specifically prevents the oxidation of the filament, the lack of observable changes in B filaments compared to the A filaments is also evident of oxidation in the unstabilized PP.

CONCLUSIONS

The following is a summary of the findings of this study of degradation in polypropylene surgical implants.

1) Infrared spectra show that pure polypropylene filaments implanted subcutaneously in hamsters degrade by an oxidation mechanism similar to that which has been found by others by the autoxidation of PP at elevated temperatures.

2) The initiation rate for the degradation process was found to be 0.061 mg OH/g PP/day. This compared with a calculated rate of 2.9×10^{-4} mg OH/g PP/day for the gas-solid phase reaction between 3.3% O₂ and PP film at 37°C.

3) Carbonyl groups were observed to form after 99 days of implantation. The induction time was determined to be approximately 108 days, using the criteria of the intersection of the lines approximating the initiation and propagation portions of the oxidation curve.

4) Dynamic mechanical tests of implanted filaments show that the rigidity increases during the first 30 days of implantation, but remains constant thereafter up to the test limit of 150 days.

5) Infrared spectra and mechanical testing of implanted and non-implanted filaments containing an antioxidant show no changes in chemical or physical properties as a result of implantation. These results support the view that the changes observed for pure implanted filaments are due to oxidation rather than diffusional or other unknown effects, since the antioxidant specifically inhibits and/or retards oxidation.

6) GPC analyses indicate that some chain scission occurs during the first 70 days of implantation, a fact which is further evidence in support of a *in vivo* autoxidative mechanism.

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